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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/393,652 | 09/10/1999 | PRAMOD K. SRIVASTAVA | 8449-025-999 | 3088 |

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| EXAMINER | |
|---|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/393,652 | SRIVASTAVA ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *54-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 3/28/06 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments, remarks, filed 3/28/06, have been entered.

2. Claims 1-53 have been cancelled.
Claims 54-71 have been added and are being acted upon.

3. The drawings filed 9/26/05 remain unacceptable and have not been entered.

Applicant has indicated in the instant Remarks the details of the changes to the Drawings. It is noted, however, that in a number of instances the substance of the Drawings has been changed. For example, the handwritten notes in the drawings have been removed, thus deleting information. Additionally, the legend for several of the Figures has been changed, e.g., the legends of Figures 1 and 2. In Figure 2 the legend previously identified four colors/patterns. The drawings of 9/26/05 identify 6 colors/patterns. In this instance information has been added.

4. In view of Applicant's amendments the previous rejection under 35 U.S.C. 112, first paragraph, for the introduction of new matter, has also been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 54-71 (replacing Claims 33-53), stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for inhibiting the rejection of BALB/cJ skin when transplanted onto a C57BL/6 mouse, said method comprising administering to a C57BL/6 mouse gp96 purified from a BALB/cJ source, said administration comprising subcutaneous injection of 100 ug 10 days prior to transplantation, repeated 3 days prior to transplantation,

does not reasonably provide enablement for:

a method for inhibiting rejection of a grafted cell, tissue, or organ in a mammal comprising administering to a mammal a composition comprising a purified complex consisting essentially of a gp96 heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cell, tissue, or organ, and wherein the composition is administered after/prior to the cell, tissue, or organ being grafted to the mammal.

As set forth previously, little is known regarding treating or preventing graft rejection by administering HSPs. Indeed, the Inventor himself has repeatedly taught that in numerous contexts, both in vitro and in vivo, all heat shock proteins are immunostimulatory (see for example, U.S. Patents No. 5,985,270, 5,750,119, and 5,961,979). Accordingly, claims based on the highly unexpected assertion that HSPs are sometimes immunosuppressive when administered in vivo, require enablement commensurate with the scope of the claims.

Regarding the scope of the claims, it is noted that said claims encompass the claimed method employing all HSPs (except hsp60 and cpn10) which Applicant has repeatedly argued (and demonstrated with sequence alignments) are not related and are not interchangeable. Clearly then, given the highly unexpected nature of the instant invention, said invention cannot be considered to be enabled for any HSP not demonstrated (in the specification or art) to be immunosuppressive in the instant context (graft rejection). It is noted that the specification discloses only the use of BALB/cJ mouse and unknown rat gp96, and only in the context of transplant into a C57BL/6 mouse. The results of Experiment 2 demonstrate that rat gp96 treatment worked little (if any) better than control (no) treatment in the instant method. Accordingly, not even all gp96's (even those likely to be closely related) can be considered to be enabled. The most likely conclusion to be drawn from the limited data is that the gp96 must derive from the same genetic source as the graft.

A review of the specification discloses that the maximum disclosed dosage range is "about 5 ug to about 5000 ug" of complex (page 31). There is no disclosure in the specification of any dosage greater than "about 5000 ug" in any context. The specification also discloses that a 20-25 g mouse is administered 100-200 ug of complex; the specification also demonstrates that lesser dosages are ineffective (see Experiments 1 and 2). As a human is roughly 3000 times the size of a mouse, the appropriate dosage for a human would likely be 300,000-600,000 ug of complex - at least 60 times higher than the highest dosage disclosed by the specification. As a horse or cow is roughly 10 times the size of a human, the maximum disclosed dosage would likely fall 600 times short of what would be required to be effective in said mammals.

It is the Examiner's position then that given the broad scope of the claims and the limited working examples, the specification cannot be considered enabling for the invention as claimed.

Applicant has submitted WO 02/072133 as enablement for "HSP70 family members" in the method of the instant claims. Upon review said document cannot be considered enabling for the use of HSP70 family members in the method of the instant claims. The document discloses the use of BiP (a HSP70) only in a highly artificial arthritis model. Presumably, Applicant's argument is that artificial arthritis and graft rejection are both TH1- mediated, thus a treatment for the artificial arthritis model would be effective as a treatment for graft rejection. The document indicates that BiP has an immunosuppressive effect because it stimulates IL-10 release (page 8) which induces an anti-inflammatory shift towards TH2 (page 23). This capability of inducing IL-10 release and the subsequent shift towards TH2 is presumably how BiP might function in inhibiting graft rejection. There exists however, a significant body of work indicating that IL-10 is not necessarily immunoprotective, a shift towards TH2 is not necessarily desirable, and a HSP70 might actually be a facilitator in numerous models of TH1-mediated pathology. See for example, Pakala et al. wherein it is taught that in a disease model thought to be TH1-mediated, induction of IL-10 and a TH2 response, rather than being protective or benign, was highly pathogenic. The work calls into question the entire concept of a shift towards TH2 as a treatment of TH1 pathologies. See also McFarland, wherein as early as 1996 it was taught the "Mechanisms of autoimmunity (and presumably graft rejection) are more complicated than a simple TH1-Th2 dichotomy". The reference further teaches additional instances wherein the TH2 response worsens diseases thought to be THI mediated. As regards an HSP70 family member specifically, Mycko et al. teaches the enhancement of another TH1 mediated disease by over-expression of HSP70 and increased Class II presentation of an autoantigen. The combined references indicate that, at best, the use of a HSP70 in a method of inhibiting a TH1-mediated response [including graft rejection] must be considered to be highly unpredictable.

In the specific context of allograft reaction, Pockley teaches that "the balance between protective and damaging effects [of HSPs] and the precise influence of these responses on graft outcome is unclear". In some instances HSPs appear to promote the development of acute and chronic graft rejection whereas in other instances heat shock proteins appear to be cytoprotective. The reference concludes that "The role of heat shock proteins in allograft immunity is unclear and more insight into the processes by which heat shock proteins encounter and are recognized by the recipient immune system after transplantation is required." Clearly then, the reference serves to define the invention of the instant claims as being unpredictable.

Applicant's arguments, filed 3/28/06, have been fully considered but they are not persuasive. Applicant argues that the establishment of effective dosages for the inhibiting of graft rejection would be routine and cites pages 31-32 of the specification.

As set forth previously, the paragraph bridging pages 31 and 32 which indicates that doses in the range of 100-200 um of gp96 for a 20-25 g mouse prevent graft rejection. "Similar high dosages of 100-200 ug, or more than 200 ug, of hsp may also be

effective in the treatment of larger mammals including humans". This comprises the *entire* disclosure of the specification regarding effective dosages in humans. Said minimal disclosure cannot be considered to be enabling for such a critical element of the claimed method. Further note, as set forth previously, that the establishment of an effective dose of HSP for immunosuppression is not a matter of simply ramping up dosages until an effective dosage is determined. In this case, it has been well-documented that HSPs are more often than not *immunostimulatory*, thus, an improper dosage would as likely kill a patient in need of immunosuppression as benefit him.

Applicant reiterates the Inventor's assertions that all HSP90 family proteins should be immunosuppressive given their structural similarity.

The instant specification *demonstrates* that Applicant's assertions are simply incorrect. See again Example 2 wherein rat gp96 is shown not to be immunosuppressive in mice.

Applicant argues that the Examiner cites Chandawarkar et al. 1999 and improperly dismisses Chandawarkar et al. 2004. Applicant submits are more recent publication by Chandawarkar et al. (Kovalchin et al., 2006).

Regarding Chandawarkar et al. 2004, the discrepancies between the 1999 findings and conclusions and the 2004 findings and conclusions are attributed to differences in immunizing dosages of antigen. This is clearly an issue that was not understood at the time of filing of the instant application. As set forth in MPEP 2164.05, a specification *must* be enabled at the time of filing. Applicant cannot submit post-filing references in an attempt to enable that which was not enabled at the time of filing because it was not understood at the time of filing. Thus, neither Chandawarkar et al. 2004 nor Kovalchin et al. 2006 can enable the method of the instant claims. And note again the teachings of Pockley 2001, "the balance between protective and damaging effects [of HSPs] and the precise influence of these responses on graft outcome is unclear". What is clear, however, is that if the method of the instant claims was not enabled in 2001, it was not enabled when the application was filed in 1999.

Applicant again argues that the demonstration in the specification of rat gp96 not being immunosuppressive was due to a low dosage being administered.

As set forth previously, Applicant chose the conditions/parameters of Experiment 2 and the data shows what it shows - that in the context disclosed in the instant specification, a context that might be encompassed by the instant claims, it was not immunosuppressive.

Applicant notes that the claims now recite a limitation that the HSP be administered after the graft.

Said new limitation is acknowledged. It is also noted that the new limitation applies to only half of the claims.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 55, 57, 58, 61, 63, and 70 (replacing Claims 33, 35, 38, 40, 44, and 50) are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Srivastava et al. (1986, IDS).

As set forth previously, Srivastava et al. teaches a method of inhibiting the rejection of a grafted cell (Meth A sarcoma) comprising administering a purified gp96 hsp complex to a mouse before the Meth A cells are grafted (see particularly page 3410, Figure 5, "20 units").
Note that the source of the hsp (new Claim 57) is irrelevant in a method of administering the hsp.

Applicant's arguments, filed 3/28/06, have been fully considered but they are not persuasive. Applicant argues that the peptides of the complexes of the prior art were alloantigens.

The gp96 hsp complexes were derived from tumors of BALB/c origin and administered to BALB/c mice (page 3407, column 2), thus they were not alloantigens.

Applicant argues that the mice of the reference were not in need of the gp96 hsp treatment.

It is the Examiner's position that the animals were in need of determining the results of the experiment. Applicant's argument that the animals were in need of rejecting the tumors is not persuasive given the well-known fact that all experimental mice are ultimately killed after these sorts of experiments.

9. The following are new grounds for rejection.

10. Claim 54-71 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) The method of Claim 54 … effective to inhibit graft rejection … wherein the composition is administered after the grafted cell, tissue or organ.

B) The method of Claim 55 … effective to inhibit graft rejection … wherein the composition is administered prior to the grafted cell, tissue or organ.

C) The method of Claim 56 … comprising administration of 100 ug or more of the hsp complexes.

Regarding A) Applicant indicates that support for the new limitations can be found at pages 11 and 31, and at pages 4 and 36 of the specification. A review of pages 11 and 31 shows support only for a method of treating or preventing graft rejection or eliciting immune tolerance wherein the composition is administered after the grafted cell, tissue or organ. At pages 4 and 36 the specification teaches only the administration of hsps, and not compositions comprising purified complexes of the claims.

Regarding B) Applicant indicates that support for the new limitations can be found at pages 11 and 31, and at pages 4, 37, and 38 of the specification. A review of pages 4, 37, and 38 shows support only for a method administering donor tissue prior

to the administration of hsps, i.e., no administration of cells or organs, and no administration of the purified complexes of the claim.

Regarding C) Applicant indicates that support for the new limitations can be found at pages 11 and 31, and at pages 4, 37, and 38 of the specification. The specification does not disclose administration of 100 ug or more of complexes. Note that original Claim 17 comprised the dosage limitation of current Claim 56 but the method was not the method of the instant claim.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.

8/18/06

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